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Postoperative Ultrasound in Kidney Transplant Recipients: Association Between Intrarenal Resistance Index and Cardiovascular Events

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Background. Doppler ultrasound, including intrarenal resistance index (RI) measurement, is a widely used modality to assess kidney transplantation (KTx) vascularization. The aim of this study is to gain insight in the associations between early postoperative RI measurements and cardiovascular events (CVEs), all-cause mortality, and death-censored graft survival. **Methods.** From 2015 to 2017, a prospective cohort study was conducted in patients in which RI measurement was performed immediately after KTx. The RI was calculated as (peak systolic velocity—end-diastolic velocity)/peak systolic velocity. End points were CVEs, all-cause mortality, and graft failure. Kaplan-Meier analyses (logrank test) were used for differences in end points. Univariate and multivariate associations were investigated by means of Cox regression analyses. **Results.** RI cutoff of 0.70 was used. We included 339 recipients, of which 271 (80%) had an RI ≤ 0.70 and 68 (20%) had an RI > 0.70. CVEs were observed in 27 (8%) patients, 27 (8%) patients died, and 17 (5%) patients had graft failure during a median follow-up of 37 months (interquartile range, 33–43). Kaplan-Meier analyses and univariate Cox regression indicated a significant association with overall CVE-free survival (hazard ratios [HR], 2.79; $P = 0.011$; logrank test, $P = 0.008$) and all-cause mortality (HR, 2.59; $P = 0.017$; logrank test, $P = 0.013$) for patients with an RI above and below 0.70. An independent association was shown between an RI > 0.70 and CVE-free survival (HR, 2.48; $P = 0.042$) when deceased donation was not included in the model. **Conclusions.** In the early postoperative period, a high RI showed to be associated with CVEs after adjustment for cardiovascular risk factors, whereas no independent association was found with overall survival and graft failure. For the interpretation of RI measurements after KTx surgery, patients' cardiovascular state should be taken into consideration.

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INTRODUCTION

Kidney transplantation (KTx) remains the treatment of choice for patients with end-stage kidney disease and early postoperative assessment of KTx vascularization is warranted. Ultrasound is the imaging modality of choice according to the *Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the care of kidney transplant recipients*, as it is noninvasive, less

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expensive compared with other imaging modalities, and does not require the administration of contrast agents.[1–3] The intrarenal resistance index (RI) is one of the routinely assessed parameters during postoperative ultrasound, and it reflects the vascular flow in the renal arteries, distal to the point of measurement.[1] However, the clinical implication of the RI remains unclear, and little is known about the clinical factors that influence RI measurements.

A previous study concluded that an increased RI in KTx recipients is associated with adverse long-term patient and graft outcomes.[4] Subsequent analyses revealed that an increased RI is a reflection of characteristics of the transplant recipient rather than of the vascular condition of the graft.[5,6] Furthermore, several small, retrospective studies have shown associations of RI with recipient age, intima-media thickness, risk for new-onset diabetes mellitus, and hemodynamic factors such as the aortic pulse pressure and aortic stiffness, which further suggests that the RI is more a representation of the cardiovascular status of the recipient.[7–10] This is also apparent from a study that showed that an increased RI after KTx is associated with cardiovascular mortality.[11] However, a potential relationship between the postoperative RI and cardiovascular events (CVEs) was not further investigated.

While Doppler ultrasound with RI measurement is routinely performed after KTx, the potential association between the *early* postoperative RI and clinical outcomes has not yet been determined. Also, there is no agreement to a standard RI in daily medical use or published research: previous studies used a cutoff between 0.70 and 0.80, based on the optimal cutoff in their specific population.[4–6,12]

We hypothesized that early postoperative RI measurements are influenced by the cardiovascular status of KTx recipients, which would result in an association between RI measurements and post-KTx CVEs. Evidence of this association will provide a better understanding of RI measurements and support clinicians with the interpretation. The aim of this study is to gain insight in the association between early postoperative RI measurements and CVEs, all-cause mortality, and death-censored graft survival.

MATERIALS AND METHODS

Patients

All adult patients (≥18 y old) who underwent Doppler ultrasound with RI measurement directly after KTx at the University Medical Center Groningen (UMCG) between November 2015 and September 2017 (n = 364) were prospectively included and retrospectively analyzed. Patients were not included for further analysis if (a) flow measurements were insufficiently reported (n = 18) or (b) patients underwent a combined liver-kidney or kidney-pancreas transplantation (n = 7), leaving 339 patients eligible for statistical analyses.

Patients' charts were screened for baseline characteristics. The primary end point was the incidence of CVEs. A CVE was defined as the occurrence of a myocardial infarction (International Statistical Classification of Diseases and Related Health Problems [ICD]-10: I21), both ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI), unstable angina pectoris (ICD-10: I20), a cerebrovascular accident (ICD: I60-I66), a transient ischemic attack (ICD-10: G45), or cardiovascular death (as death due to one of the afore mentioned circulatory conditions).[13] Secondary outcomes were (a) all-cause mortality and (b) death-censored graft failure. Graft failure was defined as end-stage kidney failure requiring the reinstitution of dialysis or a retransplantation. Kidney transplant recipients who died with a functioning graft were censored at time of death. Delayed graft function (DGF) was defined as the requirement of dialysis within the first week after transplantation. Associations were determined for both 1-year outcomes and overall follow-up outcomes. To ascertain the incidence of CVEs, all-cause mortality, and graft failure, the electronic hospital registry was consulted. In case of inconclusive or missing follow-up data, the concerning general practitioner was approached.

This study was registered in the UMCG research register. Due to the descriptive character of this study, our institution's Medical Ethics Committee granted a dispensation for the Dutch law regarding patient-based medical research (WMO) obligation (Medical Ethical Committee UMCG—201800363). Patient data were processed and electronically stored according to the Declaration of Helsinki for medical research involving human subjects. The clinical and research activities were consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism."

Doppler Ultrasound

According to hospital protocol, the arterial intrarenal RI was measured 3 times (in the upper pole, interpolar, and lower pole) within 3 hours after surgery, in each KTx recipient. These indices were determined in the interlobar or arcuate arteries. The arterial RI was calculated as (peak systolic velocity—end-diastolic velocity)/peak systolic velocity. For each patient, intrarenal RI was then calculated as mean of these 3 measurements. The observation of postoperative perinephric fluid collections (hematoma, urinoma, lymphocele) and hydronephrosis was based on the description in the postoperative ultrasound report at time of RI measurement. The ultrasound procedure was performed with a curved array transducer (multifrequency, 1–6 MHz) on a Toshiba Aplio MX (Tokyo, Japan) or Zonare ZS3 (Shenzhen, China) ultrasound system.

Statistical Analyses

The RI cutoff for the presented analysis was determined using the highest area under the receiver operating characteristics curve and the Youden Index.[14] The Youden Index is a statistic that presents the performance of a dichotomous diagnostic test and is calculated as (sensitivity of the test + specificity of the test) – 1. Baseline descriptive statistics are presented as mean (±SD) or median (interquartile range, IQR) for continuous variables and counts with percentages for categorical variables. Differences in baseline characteristics were tested with the unpaired *t*-test, Mann-Whitney *U* test, and Chi-squared test, depending on type and distribution of the data. A Kaplan-Meier curve and logrank test were performed to identify differences in the incidence of CVE-free survival, patient survival, and death-censored graft survival between the 2 groups. Univariate Cox regression analyses were performed to calculate hazard ratios (HRs) as estimates of relative risks. Multivariate Cox proportional hazard regression analyses were performed for the calculation of risks, including the following predetermined potential explanatory variables:

recipient age, gender, body mass index, smoking status, diabetes, preoperative systolic blood pressure and diastolic blood pressure (DBP), use of antihypertensive drugs, preoperative cholesterol, statin use, pretransplant dialysis, dialysis vintage, history of hypertension, history with cardiovascular disease (CVD), deceased donation, DGF, and an increased RI. Tests with a *P* value of <0.05 were considered significant. Data analysis was performed using IBM SPSS Statistics 23 and GraphPad Prism 7.02 for Windows.

RESULTS

Baseline Characteristics

A total of 339 kidney transplant recipients were included. At baseline, mean age (±SD) was 54 ± 15 years, and 206 (61%) patients were male (Table 1). A preemptive transplantation was performed in 101 (30%) recipients. Sixty-eight (20%) patients had a history of smoking, and 80 (24%) had experienced prior CVD. The distribution in terms of donor type was 199 (59%) living kidney donors, 63 (19%) donations after brain death, and 77 (23%) donations after circulatory death.

The median time between KTx and RI measurement was 54 minutes (IQR, 31 min to 1 h 28 min). Mean intrarenal RI was 0.64 ± 0.08. For this cohort, an RI value of 0.70 resulted in the highest area under the receiver operating characteristics curve of 0.77. The cutoff of 0.70 had a higher Youden Index compared with a cutoff of, respectively, 0.75 and 0.80 (Youden Index of 0.53 compared with 0.18 and 0.12, respectively). We stratified our cohort into 2 groups, based on the RI cutoff of 0.70. A total of 271 (80%) patients had an RI below or equal to 0.70, and 68 (20%) had a postoperative RI above 0.70. Recipients with an RI > 0.70 were significantly older, were more often dialysis dependent, had a lower DBP, and had more often a history of diabetes. (Table 1). Donors in the RI > 0.70 group were significantly older and more often involved in deceased donor transplantation compared with those in the RI ≤ 0.70 group (Table 1). In univariate linear regression analysis, a higher recipient age (ß = 0.28; $P < 0.001$), a history of diabetes (ß = 0.19; $P = 0.001$), a history of CVD (ß = 0.12; $P = 0.028$), a lower preoperative DBP (ß = –0.23; $P < 0.001$), and dialysis dependency (ß = 0.20; $P < 0.001$) were significantly associated with a higher RI (Table 2). The following donor variables were significantly associated with an increased RI: donor age (ß = 0.12; $P = 0.030$), deceased donation (ß = 0.29; $P < 0.001$), and cold ischemia time (ß = 0.25; $P < 0.001$).

In the postoperative course, DGF was observed in 58 (17%) out of 339 recipients, of which 37 out of 271 (14%) in the RI ≤ 0.70 group and 21 out of 68 (31%) in the RI > 0.70 group ($P = 0.001$). DGF was associated with the RI in linear regression (ß = 0.19; $P < 0.001$). Four (1%) recipients had a primary nonfunctioning transplant, of which 3 (1%) in the RI ≤ 0.70 group and 1 (1%) in the RI > 0.70 group. At the first

TABLE 1.

Donor and recipient characteristics

Characteristics	Overall, n = 339	RI ≤ 0.70, n = 271	RI > 0.70, n = 68	*P*
Resistance index	0.64 ± 0.08	0.61 ± 0.06	0.76 ± 0.04	
Recipient				
Age (y)	54 ± 15	52 ± 15	61 ± 12	<0.001[a]
Sex (male)	206 (61%)	159 (59%)	47 (69%)	0.12[b]
BMI (kg/m^2)	26 ± 4	26 ± 4	26 ± 4	0.65[a]
First transplantation	295 (87%)	234 (86%)	61 (90%)	0.46[b]
Smoking history	68 (20%)	60 (22%)	8 (12%)	0.061[b]
History of diabetes	64 (19%)	38 (14%)	26 (38%)	<0.001[b]
Hypertension history	198 (58%)	160 (59%)	38 (56%)	0.64[b]
CVD history	80 (24%)	61 (23%)	19 (28%)	0.35[b]
Preoperative systolic blood pressure	142 ± 21	143 ± 20	145 ± 23	0.48[a]
Preoperative diastolic blood pressure	81 ± 13	81 ± 12	78 ± 15	0.041[a]
Use of antihypertensive drugs	252 (74%)	200 (74%)	52 (76%)	0.69[b]
No. of classes of antihypertensive drugs	1.30 ± 0.91	1.28 ± 0.91	1.37 ± 0.95	0.48[a]
Preoperative total cholesterol	4.84 ± 1.04	4.89 ± 0.06	4.62 ± 0.14	0.082[a]
Statin use	101 (31%)	80 (30%)	21 (33%)	0.60[b]
Prior dialysis	238 (70%)	182 (67%)	56 (82%)	0.012[b]
Dialysis vintage (mo)	30 ± 26	31 ± 28	27 ± 17	0.24[a]
Donor				
Age (y)	54 ± 13	53 ± 14	57 ± 13	0.017[a]
Male sex	182 (54%)	145 (54%)	37 (54%)	0.89[b]
Deceased donation	140 (41%)	95 (35%)	45 (66%)	<0.001[b]
DBD	63 (45%)	42 (44%)	21 (47%)	0.79[b]
DCD	77 (55%)	54 (56%)	23 (51%)	0.011[b]
Perioperative				
Cold ischemia time (hh:mm)	6:59 ± 5:40	6:24 ± 5:32	9:18 ± 5:39	<0.001[a]
First warm ischemia time (min)	6 ± 7	5 ± 7	6 ± 8	0.34[a]
Second warm ischemia time (min)	41 ± 13	40 ± 13	43 ± 14	0.24[a]

[a]Unpaired t-test.
[b]Chi-squared test.
Data are presented as n (%) or mean ± SD.
BMI, body mass index; CVD, cardiovascular disease; DBD, donation after brain death; DCD, donation after circulatory death; RI, resistance index.

TABLE 2.

Linear regression with patient characteristics and the resistance index

	Resistance index		
	β-coefficient	t-value	*P*
Recipient			
Age recipient (y)	0.28	5.42	<0.001*
Sex recipient (female)	−0.06	−1.14	0.26
BMI recipient (kg/m²)	0.05	0.86	0.39
Smoking history	−0.14	−0.25	0.80
History of diabetes	0.19	3.47	0.001*
History of cardiovascular disease	0.12	2.20	0.028*
Preoperative systolic blood pressure	0.03	0.60	0.55
Preoperative diastolic blood pressure	−0.23	−4.26	<0.001*
Use of antihypertensive drugs	−0.11	−0.20	0.84
No. of classes of antihypertensive drugs	−0.21	−0.36	0.72
Preoperative total cholesterol	0.04	0.66	0.51
Statin use	−0.06	−1.16	0.25
Prior dialysis	0.20	3.74	<0.001*
Dialysis vintage (mo)	−0.03	−0.44	0.66
Donor			
Age donor	0.12	2.18	0.030*
Sex donor (female)	−0.11	−0.19	0.85
Type of donation (deceased)	0.29	5.62	<0.001*
Perioperative			
Cold ischemia time (h)	0.25	4.78	<0.001*
First warm ischemia time (min)	0.06	1.09	0.28
Second warm ischemia time (min)	−0.001	−0.12	0.99
Delayed graft function	0.19	3.61	<0.001*

*$P < 0.05$.
BMI, body mass index.

postoperative ultrasound, 22 (6%) patients had a hematoma, of which 18 out of 271 (7%) in the RI≤0.70 group and 4 out of 68 (6%) in the RI>0.70 group. One patient had a urinoma, and 1 patient had a lymphocele; both were in the low RI group. Three patients out of 339 (1%) had postoperative hydronephrosis, already present at time of postoperative ultrasound, of which 2 (1%) in the RI≤0.70 group and 1 (1%) in the RI>0.70 group.

Cardiovascular Events

In the first postoperative year, 11 (3%) recipients had a CVE. The 1-year CVE-free survival was significantly lower in patients with an RI>0.70 compared with patients with an RI≤0.70 (respectively, 93% versus 98%; logrank test, $P = 0.03$; Figure 1A). After a median follow-up of 37 months (IQR, 33–43), 27 (8%) of the recipients had a CVE: 10 out of 68 (15%) patients in the RI>0.70 group and 17 out of 271 (6%) patients in the RI≤0.70 group. The distribution of *first* CVEs was as follows: 6 ischemic cerebrovascular incidents, 8 unstable angina pectoris patients with the requirement of percutaneous coronary intervention or coronary artery bypass grafting, 11 (N)STEMIs, 1 transient ischemic attack, and 1 cardiovascular death. Patients with an RI>0.70 had worse overall CVE-free survival compared with patients with an RI≤0.70 (respectively, 85% versus 94%; logrank test, $P = 0.008$; Figure 2A). Univariate Cox proportional hazard regression revealed that an RI above 0.70 was associated with a worse CVE-free survival (HR, 2.79; 95% Confidence Interval [CI], 1.27-6.13]; $P = 0.011$; Table 3). In multivariate Cox regression, an RI above 0.70 was associated with CVE-free survival (HR, 2.48; 95% CI, 1.04-5.96; $P = 0.042$), independent of recipient age, gender, a positive smoking history, the use of antihypertensive drugs, a history of CVD, prior dialysis, and DGF (Model 5; Table 4). After additional adjustment for deceased donation, the RI was not significantly associated with CVE-free survival (HR, 2.08; 95% CI, 0.87-4.98; $P = 0.10$; Model 6; Table 4).

Patient Mortality

In the first postoperative year, 7 (2%) recipients died. In the group with an RI>0.70, 5 out of 68 (7%) patients died compared with 2 out of 271 (1%) patients with an RI≤0.70. The 1-year patient survival was significantly lower in patients with an RI>0.70 compared with patients with an RI≤0.70 (respectively, 93% versus 99%; logrank test, $P = 0.001$; Figure 1B). After a median follow-up of 37 months, 27 patients (8%) died, of whom 5 (19%) died from CVD. Of these 27 events, 10 (15%) occurred in the RI>0.70 group, and 17 (6%) occurred in the RI≤0.70 group. Patients with an RI>0.70 had significantly worse overall survival compared with patients with an RI≤0.70 (respectively, 85% versus 94%; logrank test, $P = 0.013$; Figure 2B). Univariate Cox proportional hazard regression showed that an RI above 0.70 is significantly associated with a worse overall patient survival (HR, 2.69; 95% CI, 1.18-5.65; $P = 0.017$; Table 3). In multivariate Cox regression analysis, the association between patient survival and an RI above 0.70 was not significant after adjustment for recipient age and gender (Model 2; Table 4).

Death-censored Graft Survival

Fourteen (4%) patients developed graft failure in the first postoperative year, of which 3 out of 68 (4%) patients with an RI>0.70 and 11 out of 271 (4%) patients with an

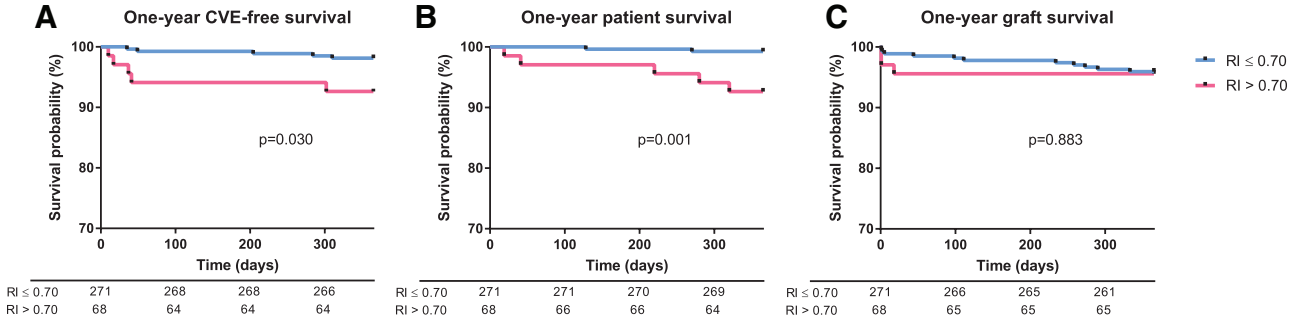

FIGURE 1. Kaplan-Meier curves of 1-y CVE-free survival, 1-y patient survival, and 1-y death-censored graft survival. CVEs, cardiovascular events; RI, resistance index.

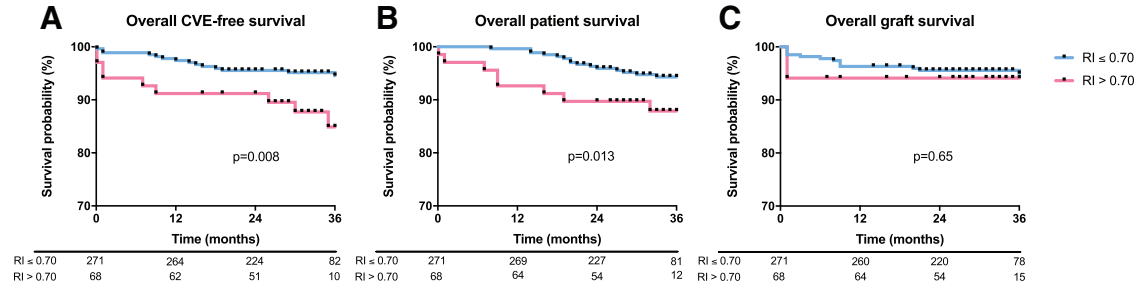

FIGURE 2. Kaplan-Meier curves of overall CVE-free survival, overall patient survival, and overall death-censored graft survival. CVEs, cardiovascular events; RI, resistance index.

RI ≤ 0.70. The 1-year death-censored graft survival did not differ between the groups (both 96%; logrank test, $P = 0.88$; Figure 1C). After a median follow-up of 37 months, 17 (5%) recipients developed graft failure, of which 4 (6%) patients in the RI > 0.70 group and 13 (5%) patients in the RI ≤ 0.70 group. The causes of graft failure were as follows: 3 acute rejection, 6 chronic rejection, 2 venous thromboses, 2 recurrences of underlying disease, 2 tubular ischemia, 1 thrombotic microangiopathy, and 1 diabetic nephropathy. The death-censored graft survival did also not differ between the groups on overall follow-up (RI ≤ 0.70: 95% versus RI > 0.70: 94%; logrank test, $P = 0.65$; Figure 2C). The RI was not associated with overall death-censored graft survival in univariate Cox regression analysis (HR, 1.29; 95% CI, 0.42-3.97; $P = 0.65$).

DISCUSSION

This study showed that KTx recipients with a postoperative RI above 0.70 had a worse CVE-free survival and lowered patient survival after 1-year and overall follow-up. We could not demonstrate any differences in death-censored graft survival between the 2 groups. Moreover, we found that an RI above 0.70 in the multivariate Cox regression analysis without inclusion of deceased donation was independently associated with a worse CVE-free survival after transplantation, whereas this independent association was not found with overall patient survival and the risk of graft failure. These findings support the hypothesis that early postoperative RI measurements are associated with, or even a representation of, the cardiovascular status of KTx recipients.

Doppler ultrasound is a noninvasive, safe, and relatively cheap imaging tool. Due to the KDIGO recommendation to evaluate the transplanted kidney with ultrasound, Doppler ultrasound is routinely performed after kidney transplantation.[3] Therefore, measuring the RI leads not to a higher patient burden but will provide the opportunity as early risk marker for CVEs and possibly patient mortality. But where the KDIGO recommendation falls short is giving an evidence-based cutoff, for example, for advising on a surgical reintervention or a patient-specific/personalized follow-up. The lack of a clear flowchart on how to interpret the duplex results, except for the gross information on perfusion or hematomas, restricts a wider implementation, especially when it is becoming clear that Doppler ultrasound data have information of both the graft and the recipient, which may provide information for patient-specific/personalized follow-up.

Our study is in line with a study that detected an increased risk of cardiovascular mortality in patients with an increased RI in the posttransplant period.[11] In this study, the RI was more associated with cardiovascular death than overall death. With only 5 patients dying from CVD in our study, we were unable to reproduce these results. The association between patients' cardiovascular state and the RI is possibly caused by the underlying mechanism of increased arterial stiffness in patients with worse cardiovascular risk profiles. An increase in a higher mean arterial pressure leads to the recruitment of inelastic collagen fibers.[15] The increase in inelastic collagen fibers leads to an increased arterial stiffness (or decrease in compliance), which causes a relative increase of the systolic blood pressure and a relative decrease of the DBP, resulting in an increased RI.[9,16]

In accordance with a large prospective study, we found associations between the RI and donor age, deceased donation, and cold ischemia time.[4] However, we found no associations between the RI and graft survival.[4] In that study, a high RI was associated with the requirement of dialysis. However, an extensive variation in time of Doppler ultrasound performance was used, ranging from 3 to 317 months. The enrolled patients could therefore have been transplanted within a time interval of a few months to many years. Interestingly, the time after transplantation in patients with a high RI was significantly higher (6.6 ± 5.5 versus 4.6 ± 4.6 y). The time elapsed after transplantation has proven to be a major determinant of the predictive value of the RI in predicting allograft failure or recipient death.[17] These factors may have led to the association between the RI and the decline in graft function in this particular study but also ensure that the short-term effect cannot be assessed. In our study, the variation in time between transplant and measurement is very limited; RI measurements were performed within 3 hours after transplantation.

We showed that patients with a higher RI were older, had more often diabetes, and were more frequently dialysis dependent, all factors known to lead to a worse cardiovascular state.[18] Various smaller studies reported associations between the RI and recipient characteristics, such as age, systolic and DBP, pulse pressure, aortic stiffness, smoking status, and abdominal aortic calcifications and the carotid intima-media thickness.[7–9] This, in combination with our results, creates important evidence that an increased postoperative RI is a reflection of cardiovascular burden instead of only a marker for the condition or microperfusion of the graft parenchyma. The RI was not significantly associated with CVE-free survival after inclusion of deceased donation in the final multivariate Cox regression model. This could be explained by the over all better patient and graft outcomes of living kidney donor transplantation compared with deceased donation, which can be partly explained by the high number of preemptive KTx

TABLE 3.

Univariate Cox regression analysis on overall CVEs and all-cause mortality

	Univariate analysis					
	CVEs			All-cause mortality		
	HR	95% CI	*P*	HR	95% CI	*P*
Age recipient (y)	1.03	1.00-1.07	0.095	1.05	1.02-1.09	0.003*
Sex recipient (female)	0.64	0.28-1.45	0.28	0.43	0.17-1.06	0.051
BMI recipient, kg/m^2	1.05	0.97-1.14	0.25	1.02	0.93-1.11	0.69
Smoking history	1.49	0.63-3.52	0.37	1.20	0.48-2.98	0.69
History of diabetes	1.40	0.56-3.48	0.47	2.74	1.26-5.99	0.011*
Preoperative SBP	1.02	1.00-1.03	0.076	1.01	1.00-1.03	0.14
Preoperative DBP	1.01	0.98-1.04	0.48	0.98	0.95-1.01	0.14
Use of AH drugs	1.84	0.63-5.33	0.26	0.64	0.29-1.43	0.28
Preoperative cholesterol	1.34	0.93-1.93	0.12	1.00	0.67-1.49	0.99
Statin use	0.83	0.35-1.97	0.68	2.22	0.75-6.51	0.15
Prior dialysis	1.50	0.60-3.71	0.38	5.36	1.27-22.62	0.022*
Dialysis vintage (mo)	1.00	0.98-1.02	0.79	1.00	0.99-1.02	0.99
History of CVD	1.48	0.65-3.38	0.35	2.06	0.94-4.50	0.070
History of hypertension	1.68	0.74-3.85	0.22	1.02	0.47-2.20	0.96
Type of donation (DD)	4.38	1.85-10.36	0.001*	2.21	1.02-4.78	0.043*
Delayed graft function	1.70	0.72-4.03	0.23	2.05	0.87-4.68	0.089
Resistance index > 0.70	2.79	1.27-6.13	0.011*	2.59	1.18-5.65	0.017*

*$P < 0.05$. AH, antihypertensive; BMI, Body Mass Index; CI, confidence interval; CVD, cardiovascular disease; CVEs, cardiovascular events; DBP, diastolic blood pressure; DD, deceased donation; HR, hazard ratio; SBP, systolic blood pressure.

TABLE 4.

Multivariate Cox regression analysis on overall CVE's and all-cause mortality

	Multivariate analysis					
	CVEs			All-cause mortality		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Model 1	2.79	1.27-6.13	0.011*	2.59	1.18-5.65	0.017*
Model 2	2.39	1.06-5.38	0.036*	1.85	0.83-4.12	0.13
Model 3	2.56	1.11-5.84	0.028*	2.02	0.90-4.54	0.088
Model 4	2.53	1.07-5.97	0.035*	1.84	0.81-4.22	0.15
Model 5	2.48	1.04-5.96	0.042*	1.85	0.80-4.25	0.15
Model 6	2.08	0.87-4.98	0.10	1.94	0.84-4.51	0.12

*$P < 0.05$.
Model 1: crude.
Model 2: adjusted for recipient age and recipient gender.
Model 3: adjusted for model 2 + history of smoking and antihypertensive drugs use.
Model 4: adjusted for model 3 + history of cardiovascular disease and prior dialysis.
Model 5: adjusted for model 4 + delayed graft function.
Model 6: adjusted for model 4 + deceased donation.
CI, confidence interval; CVEs, cardiovascular events; HR, hazard ratio; RI, resistance index.

recipients undergoing living kidney donor transplantation.[19] To reliably establish the effect of RI on graft function, studies should focus on the alteration of the RI in the postoperative setting, given the scarce and somewhat contradictory evidence on the prediction of renal allograft function or graft loss with just a single RI measurement. With the information that the RI may fluctuate during follow-up and that this change can be predictive for graft function, this simple and cheap new tool can be added to our armamentarium in monitoring and adjusting the posttransplant course.[17,20]

Some limitations of the present study need to be addressed. First, the postoperative RI measurement was performed by the Radiology clinician on call, instead of 1 dedicated radiologist. The effect of this limitation on the presented results is considered minimal, in light of the low intraobserver and interobserver variability (<5%) found in the literature.[4,5] Second, the incidence of CVEs in our study can be considered low, with a CVE in 8% of patients after a median follow-up of 37 months. The numbers are comparable to the MECANO study, a prospective clinical trial in the Dutch transplant population, which reported an incidence of cardiovascular events of 11% after 7 years.[21] The design of this study creates the risk of an underestimation of the total number of CVEs, due to underreporting from follow-up centers despite the additional information that was obtained from the general practitioner.

Third, the relatively small number of patients and subsequent events left open the possibility of either a type 1 or type 2 bias. Finally, this study was conducted in a single center. The population of the study consists of relatively young transplant recipients, with a relatively high rate of living donors.

The presented results are not necessarily generalizable to KTx recipients from centers with different populations. However, the current study population corresponds to the average Dutch KTx population at this time point.[21] Another important factor that should be addressed is the used cutoff value of the RI. In the literature, the RI cutoff varies from 0.70 to 0.80.[4–6,12] This variation is probably caused by (a) the method of measuring the RI, for example, different ultrasound machines or (b) a different patient population. Multiple RI cutoff values should be evaluated to establish the optimal RI cutoff value that maximizes the generalizability and thereby the clinical value of the RI. This should ideally be incorporated into national and international recommendations or guidelines.

In conclusion, a postoperative RI above 0.70 is associated with worse CVE-free survival and to a lesser extent, patient survival. Evidence of this association provides a better understanding of RI outcomes, which can support clinicians with the interpretations of the RI. The cardiovascular status of KTx recipients should be included in the clinical interpretation of early postoperative RI outcomes and follow-up.

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